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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,076	LEPPLA ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 24, 40, 41 and 49 have been amended. Claims 1-49 are pending and under consideration.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-6, 8, 11, 12, 17, 20-22, 24-30, 32, 34, 35, 40-47 under 35 U.S.C. 103(a) as being unpatentable over Leppla et al (WO 01/21656) in view of Leppla et al (U.S. 5,677,274) and Frankel et al ('Peptide Toxins Directed at the Matrix Dissolution Systems of Cancer Cells', In: Protein and Peptide Letters, 2002, vol. 9, pp. 1-14) is maintained for reasons of record..

Claim 1 is drawn to a nucleic acid comprising residues 1-388 of DT, wherein the native furin cleavage site has been substituted for a cleavage site of a matrix metalloproteinase or a plasminogen activator and, a heterologous polypeptide, wherein the heterologous polypeptide specifically binds to a protein over expressed on the surface of a cell. Claim 2 embodies the nucleic acid of claim 1 wherein the matrix metalloproteinase is selected from the group consisting of MMP-2 (gelatinase A), MMP-9 (gelatinase B) and membrane type 1 MMP (MT1-

MMP). Claim 3 embodies the nucleic acid of claim 1, wherein the plasminogen activator is selected from the group consisting of tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). Claim 4 embodies the nucleic acid of claim 1 wherein the metric metalloproteinase cleavage sites are GPLGMLSQ and GPLGLWAQ. Claim 5 embodies the nucleic acid of claim 1 wherein the plasminogen activator site is selected from the group consisting of QRGRSA, GSGRSA and GSGKSA. Claim 6 embodies the nucleic acid of claim 1, wherein the protein over expressed on the surface of a cell is a receptor. Claim 12 embodies the nucleic acid of claim 6 wherein the cell is a cancer cell. Claim 12 embodies the nucleic acid of claim 12 wherein the cancer is leukemia. Claim 22 specifies that the leukemia is AML. Claim 8 embodies the nucleic acid of claim 1 wherein the heterologous polypeptide comprises a growth factor.

Claim 11 is drawn to a vector comprising the nucleic acid of claim 1. Claim 20 is drawn to a host cell comprising the vector of claim 11.

Claim 17 is drawn to a polypeptide encoded by the nucleic acid of claim 1.

Claim 24 is drawn to a method of treating cancer comprising administering to a subject a DT fusion protein comprising residues 1-388 of DT, wherein the native furin cleavage site has been substituted for a cleavage site for a matrix metalloproteinase or a plasminogen activator and a heterologous polypeptide which specifically binds to a protein over expressed of the surface of a cell. Claim 25 embodies the method of claim 24 wherein the matrix metalloproteinase is selected from the group consisting of MMP-2 (gelatinase A), MMP-9 (gelatinase B) and membrane type 1 MMP (MT1-MMP). Claim 26 embodies the method of claim 24, wherein the plasminogen activator is selected from the group consisting of tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). Claim 27 embodies the method of claim 24 wherein the metric metalloproteinase cleavage sites are GPLGMLSQ and GPLGLWAQ. Claim 28 embodies the method of claim 24 wherein the plasminogen activator site is selected from the group consisting of QRGRSA, GSGRSA and GSGKSA. Claim 29 embodies the method of claim 24, wherein the protein over expressed on the surface of a cell is a receptor. Claim 30 embodies the method of claim 24 wherein the cell is a cancer cell. Claim 34 embodies the method of claim 30, wherein the cancer is leukemia. Claim 25 specifies that the leukemia is

AML. Claim 32 embodies the method of claim 24 wherein the heterologous polypeptide comprises a growth factor.

Claim 40 is drawn in part to a method of targeting a compound to a cell over expressing a growth factor receptor comprising administering to the cells a DT fusion protein comprising residues 1-388 of DT, wherein the native furin cleavage site has been substituted for a cleavage site for a matrix metalloproteinase or a plasminogen activator and a heterologous polypeptide which specifically binds to a growth factor receptor. Claim 41 embodies the method of claim 40 wherein the cell expresses matrix metalloproteinase, a t-PA or a u-PA. Claim 42 embodies the method of claim 40 wherein the matrix metalloproteinase is selected from the group consisting of MMP-2 (gelatinase A), MMP-9 (gelatinase B) and membrane type 1 MMP (MT1-MMP). Claim 43 embodies the method of claim 40, wherein the plasminogen activator is selected from the group consisting of tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). Claim 44 embodies the method of claim 40 wherein the metric metalloproteinase cleavage sites are GPLGMLSQ and GPLGLWAQ. Claim 45 embodies the method of claim 40 wherein the plasminogen activator site is selected from the group consisting of QRGRSA, GSGRSA and GSGKSA. Claim 46 embodies the method of claim 40, wherein the cell is leukemia cell. Claim 47 specifies that the leukemia cell is an AML cell.

Leppla et al (WO01/21656) teaches a method of targeting a cell over expressing matrix metalloproteinase or plasminogen activator, wherein said cells include cancer cells such as leukemia and myelogenous leukemia, comprising administering to said cells a recombinant anthrax protein wherein said protein comprises matrix metalloproteinase cleavage sites, plasminogen activator cleavage sites in place of the native furin-recognized cleavage site (page 6, line 1 to page 7, line 8 and page 7, lines 23-27, page 13, lines 23-26). Leppla et al teach a specific embodiment wherein said recombinant protein comprises a heterologous receptor binding domain which is a growth factor (page 7, lines 19-22). Leppla et al teach that the recombinant proteins kill tumor cells without serious damage to normal cells (page 13, lines 29-33).

Leppla et al ('274) teach that any specific protease site can be introduced into any natural or recombinant toxin, including diphtheria toxin, for which proteolytic cleavage is required (column 10, lines 28-51).

Frankel et al teach that DT comprises an N-terminal catalytic domain, a furin-sensitive loop and a translocation domain (amino acids 1-388) followed by a cell-binding domain (amino acids 389-535) (page 8, lines 1-6). Frankel et al teach that the cell binding domain of DT binds to heparin-binding epidermal growth factor-like growth factor undergoes internalization via clatherin-coated pits and furin cleavage and the catalytic domain is then transferred into the cytosol resulting in ADP-ribosylation of elongation factor-2 and inactivation of protein synthesis and cell death (page 8, lines 6-12). One of skill in the art would reasonable ascertain that the cell binding domain of native DT did not exert cell-type specificity because heparin-binding epidermal growth factor does not exhibit cell type specificity. Frankel et al teach the fusion of the catalytic and translocation domains of DT without the cell binding domain of DT fused to u-PA , but notes the damage to human endothelial cells in vitro. It is noted that the fusion protein described by Frankel et al retained the native furin cleavage site.

It would have been prima facie obvious at the time that the claimed invention was made to substitute residues 1-388 of DT, wherein said DT had been recombinantly engineered in a similar manner as the anthrax toxin to replace the furin cleavage site with matrix metalloproteinase cleavage sites, or plasminogen activator cleavage sites, wherein the recombinant DT was also a fusion protein with a growth factor, for binding to cells which over express said growth factor. One of skill in the art would have been motivated to do so by the teachings of Leppla et al ('274) on the substitution of any specific protease site within a natural or recombinant toxin, such as DT, and the teachings of Frankel et al on the catalytic and translocation domains of DT in addition to the location of the furin cleavage sites. One of skill in the art would have been motivated to leave out the cell binding domain of DT (residues 389-535) because said cell binding domain would lead to non-specific binding and substitute the growth factor in order to target cell or cancer cells which over express growth factor receptors.

The rejection of claims 1-13, 16-36, 39-48 under 35 U.S.C. 103(a) as being unpatentable over Leppla et al (WO 01/21656), Leppla et al (U.S. 5,677,274) and Frankel et al ('Peptide Toxins Directed at the Matrix Dissolution Systems of Cancer Cells', In: Protein and Peptide Letters, 2002, vol. 9, pp. 1-14), as applied to claims 1-6, 8, 11, 12, 17, 20-22, 24-30, 32, 34, 35, 40-47 above, and further in view of Frankel et al (Clinical Cancer Research, May 2002, Vol. 8,

pp. 1004-1013) and Scherrer et al (British Journal of Haematology, 1999, Vol. 105, pp. 920-927) is maintained for reasons of record..

Claim 7 embodies the nucleic acid of claim 1 wherein the heterologous protein comprises a cytokine. Claim 13 specifies that the heterologous polypeptide comprises GM-CSF. Claim 9embodies the nucleic acid of claim 1 wherein the heterologous protein is selected from a group including GM-CSF. Claim 10 embodies the method of claim 1 wherein the nucleotide sequence is elected from SEQ ID NO:2-13. Claim 18 embodies the polypeptide encoded by the nucleic acid of claim 10, SEQ ID NO:2. Claim 23 is drawn to a pharmaceutical composition comprising the protein of claim 18 and a pharmaceutically acceptable carrier.

Claim 16 is drawn to a nucleic acid encoding a D fusion protein comprising residues 1-388 of DT wherein the native furin cleavage site has been substituted for a cleavage site for a u-PA and GM-CSF. Claim 19 is drawn to the polypeptide encoded by the nucleic acid of claim 16. Claim 31 embodies the method of claim 24 wherein the heterologous polypeptide comprises a cytokine. Claim 36 embodies the method of claim 31 wherein the heterologous polypeptide comprises GM-CSF. Claim 33 specifies that the fusion protein is encoded by a nucleotide sequence selected from SEQ ID NO:2-13.

Claim 39 is drawn to the method of claim 24 wherein the DT fusion protein comprises residues 1-388 of DT wherein the native furin cleavage site has been substituted for a cleavage site for a u-PA, and GM-CSF.

Claim 40 specifies that the heterologous polypeptide specifically binds to a cytokine receptor. Claim 48 embodies the method of claim 40 wherein the DT fusion protein comprises residues 1-388 of DT wherein the native furin cleavage site has been substituted for a cleavage site for a u-PA and GM-CSF.

Claim 49 is drawn in part to an isolated nucleic acid selected from a group consisting of SEQ ID NO:2-13..

The combination of Leppla et al (WO 01/21656), Leppla et al (U.S. 5,677,274) and Frankel et al render obvious the instant claims to the extent that the engineered DT fusion protein comprises a growth factor. The combination does not provide for an engineered DT fusion protein which comprises as the heterologous protein, GM-CSF.

Frankel et al (2002) teach the administration of a DT fusion protein wherein the heterologous protein is GM-CSF,. One of skill in the art would reasonable conclude that the DT of Frankel comprised the native furin binding site. Frankel et al teach that the DT fusion protein provided a low level of clinical activity in patients with chemoresistant AML, and that liver toxicity precluded dose escalation. Frankel et al teach that this low level of activity was in contrast to the high level of activity exhibited against cultured cells (page 1012, bridging paragraph between the first and second columns). Frankel et al suggest that liver toxicity was due to the GM-CSF binding Kuffer cells (page (1011, second column, first paragraph).

The abstract of Scherrer et al teaches that leukemic cells from patients with AML exhibited high enzymatic activity for u-PA.

It would have been prima facie obvious to provide the nucleic acid encoding the engineered DT protein rendered obvious by the combination of Leppla et al (WO 01/21656), Leppla et al (U.S. 5,677,274) and Frankel et al wherein the furin cleavage sites were replaced by u-PA cleavage sites and wherein the heterologous protein was GM-CSF. One of skill in the art would have been motivated to do so by the teaching of Frankel et al (2002) on the low level of clinical activity associated with the DT-GM-CSF fusion protein and the potential for liver toxicity, and the teachings of abstract of Scherrer et al on the high level of u-PA enzymatic activity associated with AML cells. One of skill in the art would understand that the use of the u-PA cleavage site in place of the furin cleavage site could further lower the dose of the DT-GM-CSF fusion protein require to treat the chemoresistant AML of Frankel et al because the AML cells over express the u-PA enzymatic activity which provides for the cleavage of the cytotoxic domain once internalized by the AML cell via GM-CSF. One of skill in the art would reasonable expect that a lower dose effective to treat AML would result in less liver toxicity due to Kuffer cell binding in the liver.

The rejection of claims 1-12, 14, 17, 20-22, 24-35, 37, 40-47 under 35 U.S.C. 103(a) as being unpatentable over Leppla et al (WO 01/21656), Leppla et al (U.S. 5,677,274) and Frankel et al ('Peptide Toxins Directed at the Matrix Dissolution Systems of Cancer Cells', In: Protein and Peptide Letters, 2002, vol. 9, pp. 1-14), as applied to claims 1-6, 8, 11, 12, 17, 20-22, 24-30,

32, 34, 35, 40-47 above, and further in view of Faller (WO 95/11699, 05-1995) is maintained for reasons of record..

Claim 9 embodies the nucleic acid of claim 1 wherein the heterologous polypeptide is selected from a group including Il-2. Claims 14 embodies the nucleic acid of claim 7, wherein the heterologous protein comprises Il-2. Claim 37 embodies the method of claim 31 wherein the heterologous polypeptide comprises Il-2. Claim 40 specifies that the heterologous polypeptide specifically binds to a cytokine receptor.

Claim 49 us drawn to an isolated nucleic acid comprising SEQ ID NO:2-18.

Faller et al teach the treatment of leukemia cells with a DAB389-Il-2 fusion toxin, wherein DAB389 comprises residues 1-189 of DT.

It would have been prima facie obvious at the time that the claimed invention was made to use Il-2 as the heterologous receptor binding protein of the engineered DT-growth factor fusion protein rendered obvious by Leppla et al (WO 01/21656), Leppla et al (U.S. 5,677,274) and Frankel et al. One of skill in the art would have been motivat4d to do so by the teachings of Faller et al on the treatment of leukemias by administration of the DT-Il-2 fusion protein.

The rejection of claims 1-6, 8-12, 15, 17, 20-22, 24-30, 32-35, 38, 40-47 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leppla et al (WO 01/21656), Leppla et al (U.S. 5,677,274) and Frankel et al ('Peptide Toxins Directed at the Matrix Dissolution Systems of Cancer Cells', In: Protein and Peptide Letters, 2002, vol. 9, pp. 1-14), as applied to claims 1-6, 8, 11, 12, 17, 20-22, 24-30, 32, 34, 35, 40-47 above, and further in view of Heimbrook et al (PNAS, 1990, Vol. 87, pp. 4697-4701).

Claim 9 embodies the nucleic acid of claim 1 wherein the heterologous polypeptide is selected from a group including EGF. Claim 15 embodies the nucleic acid of claim 8 wherein the heterologous polypeptide comprises EGF. Claim 38 embodies the method of claim 32 wherein the heterologous polypeptide comprises EGF.

Heinbrook et al teach fusion proteins with toxins, wherein the heterologous polypeptide is TGF-alpha which is a ligand for the EGF receptor (page 4697, first paragraph under the abstract). Heimbrook et al teach that many tumors possess EGFR and some tumor types exhibit

increased numbers of EGFR relative to normal tissue making the EGFR an attractive target for delivery of an anticancer agent (page 4697, first column, lines).

It would have been prima facie obvious at the time that the claimed invention was made to provide for an engineered DT fusion protein which comprises as the heterologous protein, EGF for binding to the EGFR. One of skill in the art would have been motivated to do so by the analogous example taught by Heinbrook et al, comprising a ligand which binds to the EGFR and a toxin moiety.

Applicant argues that the instant claims are not obvious over the prior art because of unexpected results. Applicant argues that because Diphtheria toxin is activated intracellularly, in contrast to anthrax toxin. applicant argues that due to the very different locations where diphtheria toxins and anthrax toxins are activated, it was unexpected that substitution of the native furin cleavage site would result in a diphtheria toxin which could be activated extracellularly. This has been considered but not found persuasive. Leppla et al ('274) teach that any specific protease site can be introduced into any natural or recombinant toxin, including diphtheria toxin, for which proteolytic cleavage is required (column 10, lines 28-51). Leppla is an inventor of the instant claims. There is nothing in the prior art to indicate that more than cleavage is required for activation of diphtheria toxin, so it would be reasonable to expect that the toxin would be activate after cleavage regardless of its location.

Applicant argues that in the method of Frankel et al, the DT fusions are cleaved an activated intracellularly, functioning only after intracellular cleavage. This has been considered but not found persuasive. The DT fusions referred to by Frankel (2002) retain the natural furin cleavage site.

Applicant argues that Scherrer et al does not provide a basis for obviousness because it teaches only that leukemic cells from patients with AML exhibited high enzymatic activity for u-PA, because it would be unexpected that u-PA could cleave diphtheria toxin extracellularly. This has been considered but not found persuasive. Leppla et al (WO01/21656) teaches a method of targeting a cell over expressing matrix metalloproteinase or plasminogen activator, wherein said cells include cancer cells such as leukemia and myelogenous leukemia, comprising administering to said cells a recombinant anthrax protein wherein said protein comprises matrix

metalloproteinase cleavage sites, plasminogen activator cleavage sites in place of the native furin-recognized cleavage site (page 6, line 1 to page 7, line 8 and page 7, lines 23-27, page 13, lines 23-26). Scherrer et al is only relied upon for data regarding the high expression of u-PA by AML cells.

Applicant also argues that the DAB389 Il-2-R peptides taught by Faller et al are cleaved and activated intracellularly. This has been considered but not found persuasive. Faller et al is discussing the peptide which retains the native furin cleavage site.

Applicant argues that it was unexpected that the diphtheria toxins of the invention are capable of undergoing cleavage in the extracellular environment. This has been considered but not fund persuasive. There is no objective evidence that cleavage of a matrix metalloproteinase sensitive site, or cleavage of a plasminogen activator sensitive site would be inhibited in the external environment of the cell.

All other rejections and objection as set forth of maintained in the prior office action are withdrawn.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643